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R E M A R K S

The Office Action dated February 2, 1988 has been carefully reviewed.

Reconsideration of the application, as amended, is respectfully requested.

Claims 1-7 and 11 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement.

In claim 14, "blood" has been inserted between "human" and "cells".

The Examiner alleged that the term "warm blood animals" is too broad. The Examiner further stated that

> "There are no in vivo experiments or clinical applications of the compound toward an animal infected with a retrovirus, therefore, basis for the claimed technology is not sufficiently supported".

Enclosed is a copy of U.S.P. 4,710,492, issued December 1, 1987 wherein the Examiner therein is the supervisor herein and wherein a similar method claim for a similar disclosure was allowed for the same applicants. Has the standard of patentability changed since December of 1987?

With respect to page 3, lines 3 et seq of the Office Action, references for the correlation of in vitro activity of nucleoside analogues against human immunodeficiency virus, HIV, with clinical efficacy against AIDS, are submitted herewith. Also described in articles

submitted herewith is in vitro activity data for a compound according to the invention called "D4T" and why this activity justifies consideration of D4T as a clinical candidate for the treatment of AIDS.

The two nucleoside analogues for which clinical efficacy has been established are AZT; Fischl et al, New England Journal of Medicine, 1987, 317, 185-191 and DDC; Yarchoan et al, Lancet, 1988, 76-81. The in vitro activity of AZT was first described by Mitsuya et al, Proceedings of the National Academy of Sciences USA, 1985, 82, 7096-7100 and that of DDC by Mitsuya and Broder, Proceedings of the National Academy of Sciences USA, 1986, 83, 1915-1922. Copies of these articles are enclosed.

The antiretroviral activity of D4T has been published by Professor Prusoff and Dr. Lin against murine leukemia virus, Lin et al, Journal of Medicinal Chemistry, 1987, 30, 440-444, and against HIV, Lin et al, Biochemical Pharmacology, 1987, 36, 2713-2718. Copies of these articles are enclosed.

The enclosed publication Herdewijn et al, Journal of Medicinal Chemistry, 1987, 30, 1270-1278 is of interest because the authors provide in vitro results for D4T from two assay systems. In the first which utilizes ATH8 cells (Table II, p. 1273), AZT is slightly more active than D4T, but is also much more toxic; as a result, AZT has a poorer therapeutic index. DDC which inhibits the virus replication by 50% at only 0.2 micromolar is considerablly more active than either D4T or AZT. In contrast, the authors' second in vitro assay system which utilized MT4 cells (Table III, p. 1275) shows that D4T and AZT have comparable activity, and

that both are considerably more potent than DDC. Because the results from different in vitro assay systems are variable, these types of experiments are use useful to identify compounds which have good potency against HIV, but are of limited utility to assign relative potency.

The above described Herdewijn et al paper states on page 1273 that the potency of D4T is comparable of that to AZT, but D4T is less toxic "which makes D4T a valuable candidate for further examination as a potential anti-HIV drug". They conclude this publication on page 1274 by indicating that it is "imperative to pursue"...D4T..." for more extensive pharmacological studies in the scope of developing and appropriate chemotherapy for retrovirus infections (i.e., AIDS)."

With the above in mind, reference is made to Cross v. Iizuka, 224 U.S.P.Q. 739 at 748 (Fed. Cir. 1985).

It is noted that Example 2 on pages 12-13 of the application concerns stimulated human peripheral blood mononuclear cells infected with HIV in the presence of 3-deoxythymidin-2'-ene. This example should be more than sufficient to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph.

The Examiner's attention is directed to two recent Board Decisions, namely Ex parte Chwang, 231 U.S.P.Q. 751 (Bd. App. & Int. 1986) (which cited Cross v. Iizuka, 224 U.S.P.Q. 739 (Fed. Cir. 1985)) and Ex parte Krepelka et al, 231 U.S.P.Q. 746.

The Examiner is apparently trying to limit applicants only to their working examples and this is improper.

See In re Anderson, 176 USPQ 331, 333 (CCPA 1973), where the Court held that

> " we do not regard §112, first paragraph, as requiring a specific example of everything within the scope of a broad claim...What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the disclosure of a broader invention. This it may not do."
>
> " It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name ever such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it."

Indeed, examples per se are not required to satisfy the requirements of 35 U.S.C. 112, first paragraph. See In re Strahilevitz, 212 USPQ 561, 562-563 (CCPA 1982); In re Stephens, 188 USPQ 659, 660-662 (CCPA 1976); In re Borkowski, 57 CCPA 946, 164 USPQ 642, 645-646 (CCPA 1970); In re Gay, 50 CCPA 725, 135 USPQ 311, 316 (CCPA 1962).

The Court held in In re Robins, 166 USPQ 552, 555-556 (CCPA 1970) that working examples are only one means of satisfying the enablement requirement of 35 U.S.C. 112, and that the mere listing of specific compounds, chemical substituents, solvents, cross-linking agents, etc. in the specification would in most cases provide suitable evidence of enablement equivalent to specific working examples utilizing each of the various components.

The disclosure as set forth by the applicants in the application must be given the presumption of correctness and operativeness by the Patent and Trademark Office. The only relevant concern of the Patent and Trademark Office is

the truth of the assertions in the application. In any event, the burden is on the Patent and Trademark Office whenever a rejection is made for lack of enablement under Section 112. The Examiner must explain why the Examiner doubts the truth or accuracy of the statements in a supporting disclosure to which the Examiner objects. The Examiner must back up such assertions with acceptable evidence or reasoning which contradicts applicants' contentions. See, for example, In re Marzoocchi, 169 USPQ 367, 369-370 (CCPA 1967) and In re Bowen, 181 USPQ 48, 50-52 (CCPA 1974).

The Examiner in the case at hand has not carried the Examiner's burden of showing the applicants' specification to be untrue or inaccurate; indeed, the Examiner gave no evidence or reasoning for the rejection.

Applicants do not believe that any experimentation would be necessary for one skilled in the art to practice their described invention. Assuming arguendo that a certain, limited degree of experimentation would be required for one skilled in that art to reproduce applicants' invention, such experimentation would not deter from applicants' satisfaction of the enablement requirement under 35 U.S.C. 112. See, for example, In re Miller, 169 USPQ 597, 602 (CCPA 1971); In re Angstadt, 190 USPQ 214, 218-219 (CCPA 1976); Ansul Company v Uniroyal, Inc., 179 USPQ 759, 763 (2d Cir. 1971), cert. denied, 172 USPQ 257 (1972); and Caldwell v. The United States, 175 USPQ 44, 47-48 (U.S. Ct. Cls. 1972).

It should be further noted that only those skilled in the art must be enabled, not the general public. In re Storrs, 114 USPQ 293, 296-297 (CCPA 1957).

Based on the above, applicants respectfully solicit withdrawal of the rejection of claims under 35 U.S.C. 112, first paragraph.

Claims 1-7 and 11 were rejected under 35 U.S.C. 103 as being unpatentable over U.S.P. 3,817,982 to Verheyden et al (Reference A) in view of Japanese 0,027,783 (Reference L) in combination with the Robins Report (Reference U).

The present invention concerns treating warm blooded animals infected with a retrovirus, e.g., HIV, by administering an anti-retroviral amount of 3'-deoxy-thymidine-2'-ene.

The abstract of Verheyden et al mentions the production of 2',3'-unsaturated nucleosides as antivirals, but does not mention retrovirus, let alone HTLV-III/LAV (HIV-I). The antiviral agents that are presently in clinical use or shown to be effective against a variety of DNA and RNA viruses are not useful against HIV-I. Therefore, it is not obvious that a compound which is active against RNA and DNA viruses will be clinically useful against the AIDS-virus.

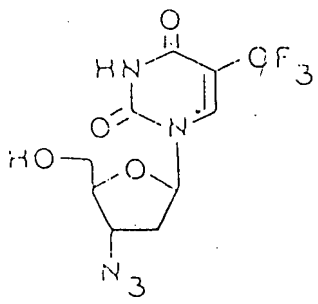
For example, ribavirin, which has very broad spectrum of antiviral activity against RNA and DNA viruses, when given to patients with AIDS in a controlled experiment resulted in more patient deaths than produced by the control-placebo.

The claims 1-29 of Verheyden et al refer only to improved methods of preparation of compounds. There is no

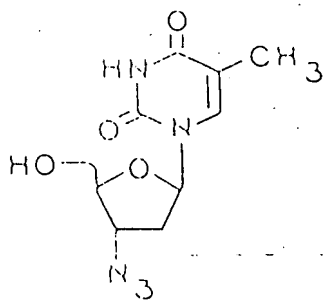
recitation for any biological activity in any of the claims. In view of the above, the Verheyden et al reference is deemed to be non-enabling with respect to treatment of retroviruses.

When Verheyden et al filed their application on December 29, 1971 that ultimately matured into their patent, there were no reported cases of AIDS (see applicants' claim 3).

Verheyden et al describe a compound which is close in structure to AZT, a compound presently used in a treatment of AIDS.



the Verheyden et al compound

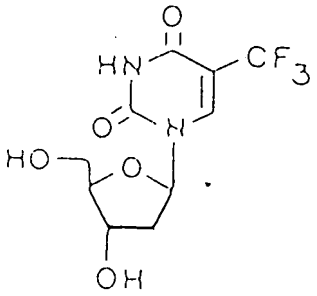


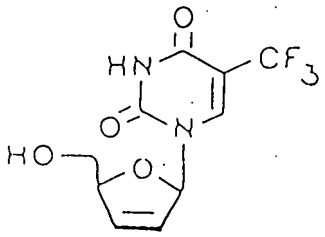
AZT

Whereas AZT is a potent antiviral against HIV-I, the Verheyden et al compound, has absolutely no activity against this virus at a concentration of more than 100 μM. AZT has an EC_{50} of 0.002 μM. See page 16 and Figure 1 of the copy of record of Lin et al, "Synthesis and Antiviral Activity of Various 3'-Azido Analogues of Pyrimidine Deoxyribonucleosides Against Human Immunodeficiency Virus (HIV-I, HTLV-III/LAV)".

Therefore, replacement of $-CH_3$ of AZT with $-CF_3$ produced an inert compound, but this was <u>not</u> obvious.

The reference cited in column 13, second paragraph in Verheyden et al indicates antiviral activity of 2',3'-dideoxy-2',3'-unsaturated trifluoromenthyluridine against the vaccinia virus, not HIV-I. As indicated above, one can not assume anti-HIV-I activity merely because it has activity with a different virus. Of relevance is the copy of record of Khwaja, T.A. and Heidelberg, C., J. Med. Chem., 12, 543 (1966) which indicates that the unsaturated trifluoromethyluridine analog was 1/1000 as active as the saturated analog, 5-trifluoromethyl-2'-deoxyuridine.

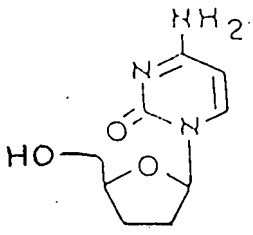


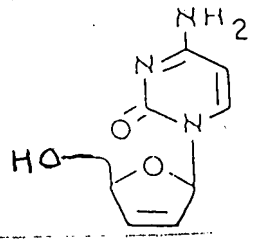


Saturated Unsaturated

Again it is therefore not obvious that the 2',3'-unsaturated analog of thymidine (compound as used in the present invention) would be markedly more active than the 2',3'-saturated analog of thymidine. Therefore, just the reverse, of what one would have predicted to be obvious, was observed.

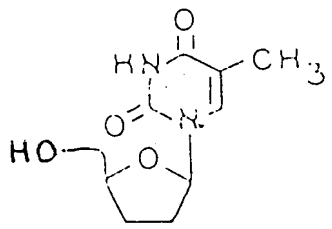
Another example of where modification of structure does not result in an obvious result is seen in a comparison of 2',3'-dideoxycytidine with 2',3'-dideoxy-2',3'-didehydrocytidine:

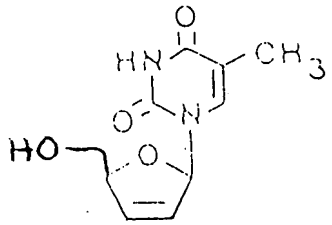




These two compounds have similar activity with EC_{50} for the saturated compound being 0.011 μM, and that for the unsaturated analog having an EC_{50} of 0.005 μM. Also see page 313 of the copy of record of Lin et al "Antiviral Activity of 2',3'-Dideoxycytidin-2'-ene (2',3'-dideoxy-2',3'-didehydrocytidine) Against Human Immunodeficiency Virus In Vitro", Biochemical Pharmacology, Vol. 31, No. 3, pp. 311-316, (1987). The difference being very slight.

However, comparison of the corresponding thymidine analogs 3'-deoxythymidine with the compound used in the present invention, 3'-deoxythymidin-2'-ene,





revealed a finding that could not have been predicted based on a comparison of the corresponding cytidine analogs. 3'-Deoxythymidine has an EC_{50} of 0.170 μM, whereas the compound used in the present invention, 3'-deoxythymidine-2-'ene, has an EC_{50} of 0.009 μM. See page 4 of the copy of record of Lin et al, "Potent and Selective In vitro Activity of 3'-Deoxythymidin-2'-ene (3'-Deoxy-2',3'-Didehydrothymidine) Against Human Immunodeficiencey Virus".

Hence, the difference in antiviral activity against HIV-I of the saturated and unsaturated cytidine analogs differed by an insignificant factor of 2, whereas the unsaturated analog of thymidine is about 19-times more potent than the saturated analog. It was not obvious that such a marked increase in activity would have been observed

based on what was found with the corresponding cytidine analogs.

The following papers, copies of which are of record, indicate variation in activity among different viruses:

(1) De Clercq , Journal of Antimicrobial Chemotherapy, 14, Suppl. A, 85-95 (1984) -see Table II on page 88

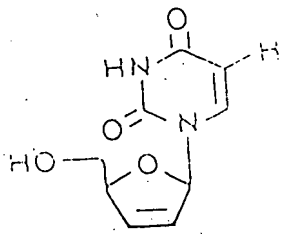
(2) Biochemical Pharmacology, Vol. 29, pp. 1849-1851

(3) Machida, Antimicrobial Agents and Chemotherapy, Vol. 29, No. 3, 524-526, Mar. 1986

(4) De Clercq et al, J. Med. Chem., 29, 213-217, (1986) - see Table. II on page 214.

The Examiner alleged that Verheyden et al teach the equivalents of 5-lower alkyl of 2',3'-unsaturated cytidin-2'-ene nucleosides. However, it is reported in Kim et al., J. Med. Chem., 30, 862, (1987), a copy of which is of record, that whereas 2',3'-dideoxycytidine is very active against HIV-I, the insertion of a $-CH_3$ moiety in the 5-position abolished its antiviral activity against HIV-I and had increased cytotoxicity.

Furthermore, removal of the $-CH_3$ moiety of the subject compound results in the formation of 2',3'-dideoxy-2',3'-didehydrouridine, a compound which has no activity against HIV-I (Herdewijn et al., J. Med. Chem., 30, 1273, (1987), a copy of which is of record). Thus again, slight modifications of structure do not necessarily result in "obvious" results.



Submitted herewith is a Declaration of Prusoff wherein there is provided a side-by-side in vitro comparison of compound 3'-deoxythymidin-2'-ene(3'-deoxy-2',3'-didehydrothymidine; d4T), used in the present invention, with the comparable compound wherein the methyl moiety (C1) was replaced with the next higher alkyl, an ethyl moiety (C2) with respect to antiviral activity against HIV-1 (the AIDS virus) in H9 cells.

The results given in the Prusoff Declaration clearly indicate potent activity when R1 is C1 (that is a methyl group) and no activity when R1 is C2 (that is an ethyl group).

Hence the most closely related compound has no activity, and therefore, it is not obvious from Verheyden et al (wherein R1 is a C3 to C7 alkyl) that a compound according to the invention (when R1 is a C1 alkyl) would have such potent antiviral activity against the AIDS virus (HIV-1).

Also submitted herewith is a declaration under Rule 132 of Dr. J.P. Sommadossi which states that 3'-deoxythymidine-2'-ene was found to be significantly less toxic than AZT (100-fold less toxic than presently used AZT) and that it was one of the most impressive anti-retroviral compounds tested.

The Japanese '783 reference is in the Japanese language and based on the English language Abstract provided by the Examiner, all that can be gleaned from this reference is that it concerns antitumor and antiviral actions. No

mention is made in the Abstract of this reference for anti-retroviral action, let alone action against HIV.

The findings of Robins that ribavirin may be active for many RNA and DNA viruses does not render obvious that a compound effective against one virus would be effective against another virus. As mentioned above, when ribavirin was given to AIDS patients in a controlled experiment, there resulted more patients deaths than produced by the control-placebo.

In view of the above, withdrawal of the rejection of claims under 35 U.S.C. 103 is earnestly requested.

Applicants believe that this application is now in condition for allowance of all claims therein, and the early issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

SPRUNG HORN KRAMER & WOODS

By Richard S. Barth
Richard S. Barth
Reg. No. 28,180

600 Third Avenue
New York, NY 10016

(212) 661-0520

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Sprung, Horn, Kramer & Woods

By Richard S. Barth

Date MAR 2, 1998